

# In the United States Court of Federal Claims

No. 07-60V

## VACCINE CASE

Filed Under Seal: November 28, 2011

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**TO BE PUBLISHED<sup>1</sup>**

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FRANK HARRIS, Parent of JORDAN  
HARRIS, a Minor,

Petitioner,

v.

SECRETARY OF HEALTH AND  
HUMAN SERVICES,

Respondent.

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Alternative Causation;  
Causation-In-Fact;  
National Childhood Vaccine Injury Act of  
1986, 42 U.S.C. § 300aa-12(e)(2);  
Pre-Existing Condition.

**Ronald Craig Homer**, Conway, Homer & Chin-Caplan, P.C., Boston, Massachusetts, Counsel  
for Petitioner.

**Voris Edward Johnson**, United States Department of Justice, Washington, D.C., Counsel for  
Respondent.

## MEMORANDUM OPINION AND FINAL ORDER

This case arises from a Motion to Review a May 27, 2011 Decision Denying Compensation in *Harris v. Sec’y of HHS*, No. 07-60V, 2011 WL 2446321 \*35 (Fed. Cl. Spec. Mstr. May 27, 2011) (“*Harris*”).

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<sup>1</sup> Pursuant to Rule 18(b) of the Vaccine Rules of the United States Court of Federal Claims (“VRCFC”), this Memorandum Opinion and Final Order was filed under seal on November 28, 2011 and “held for 14 days to afford each party the opportunity to object to the public disclosure of any information furnished by that party.” VRCFC 18(b).

## I. RELEVANT FACTS.<sup>2</sup>

### A. Medical Records.

Jordan Harris was born on March 6, 2004. Pet. Ex. 2 at 3. On March 17, 2004, Jordan's pediatrician found him to be a "well child" after his first visit. Pet. Ex. 4 at 137-38. On May 7, 2004, Jordan received his first set of immunizations, including the DTaP vaccine.<sup>3</sup> Pet. Ex. 5 at 2. Jordan's mother recalled that, after the vaccination:

Jordan's father and I brought him home, and after a few hours we noticed discomfort in his legs from the shots. He was crying uncontrollably. Our pediatrician recommended infant Tylenol to ease the pain. After we did this, he gained some relief and took a nap for approximately 1 hour. . . . Jordan's first seizure happened several hours after receiving his immunizations. At this time, Jordan had a fever of 101 degrees. He had a fixated stare and emanated grunting noises. This lasted for approximately 5-10 minutes, then his eyes rolled back in his head.

Pet. Ex. 12 ¶¶ 4-5.<sup>4</sup>

Around 8:00 p.m. that same day, Jordan was taken to the Emergency Room at the Metropolitan Hospital Center in New York City where he was admitted in stable condition. Pet. Ex. 4 at 17-18. On admission his fever was recorded at 101.1 degrees and he was diagnosed as having a seizure and a fever. Pet. Ex. 4 at 17-18. Jordan was given a physical examination and the Progress Record noted: "[Seizure] episode vs[.] [vaccine] reaction." Pet. Ex. 4 at 29. On May 9, 2004, Jordan was discharged. Pet. Ex. 4 at 41.

On July 7, 2004, Jordan received a four-month set of immunizations, including a second dose of DTaP. Pet. Ex. 5 at 2. On September 3, 2004, Jordan received a six-month set of immunizations, including a third dose of DTaP. Pet. Ex. 5 at 2. There is no indication that Jordan suffered any seizures as a result of, or had any other adverse reactions to, either of these vaccinations.

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<sup>2</sup> The relevant facts in this opinion were recited in *Harris*, 2011 WL 2446321 at \*\*1-3 as derived from Petitioner's Appendix of Exhibits ("Pet. Exs. 1-74"); Respondent's ("Government's") Appendix of Exhibits ("Gov't Exs. A-WW" and "Gov't Trial Ex. 1"); and an Evidentiary Hearing on October 8-9, 2009 ("TR 1-594").

<sup>3</sup> DTaP is the acronym for the "diphtheria and tetanus toxoids and acellular pertussis vaccine." DORLAND'S ILLUSTRATED MEDICAL DICTIONARY 568 (32nd ed. 2011) ("DORLAND").

<sup>4</sup> The admissions note from Metropolitan Hospital Center includes a patient history obtained from Jordan's mother indicating that Jordan received his vaccinations at 10:00 a.m., was given Tylenol in response to irritability at 1:30 p.m., and began experiencing a seizure at 5:30 p.m. Pet. Ex. 4 at 26.

On September 28, 2004, Jordan experienced a second seizure while taking a bath. Pet. Ex. 12 ¶ 7. He was admitted to the Connecticut Children's Medical Center in Hartford, Connecticut, where he was examined by a neurologist. Pet. Ex. 7 at 87. The Progress Notes described Jordan as having a febrile seizure after his first set of immunizations, but with no family history of seizures. Pet. Ex. 7 at 46-47. A magnetic resonance imaging ("MRI")<sup>5</sup>, computed tomography scan ("CT scan")<sup>6</sup>, and electroencephalogram ("EEG")<sup>7</sup> were taken, but found to be normal, and Jordan was discharged from the hospital. Pet. Ex. 7 at 47 (MRI), 74 (CT scan), 76 (EEG).

On October 22, 2004, Jordan had another seizure. Pet. Ex. 12 ¶ 8. On November 30, 2004, Jordan returned to the Emergency Room at the Connecticut Children's Medical Center after another seizure and with a temperature of 101.2 degrees. Pet. Ex. 7 at 20. He was discharged that same day with a diagnosis of seizure, fever, and diarrhea. Pet. Ex. 7 at 18.

On February 3, 2005, Jordan was examined by Dr. Carol Leicher, M.D., a Neurologist at Connecticut Children's Medical Center. Pet. Ex. 6 at 67-68. Dr. Leicher noted:

Jordan has a normal neurological examination. He has had seizures which are focal at times and have involved either side of his body and also some generalized seizure activity, which occurred in the context of a fever. His workup has been negative, and his development has been normal. My feeling is that he should probably be on anticonvulsant medication, if we would like to try to prevent further seizures. The fact that he has had a total of 6 seizures over the past 9 months is suggestive of the likelihood of more seizures in the future, at least until his brain becomes more mature. I do not feel he needs any further evaluation because he has had more than [one] EEG that was negative, and he has had imaging studies, as well as some metabolic studies which were unrevealing.

Pet. Ex. 6 at 67-68.

On February 4, 2005, Jordan saw Dr. Lee Hoffman, M.D., a Pediatrician at the Children's Medical Group in Bloomfield, Connecticut, who noted that Jordan had good weight gain, but a seizure disorder. Pet. Ex. 5 at 26.

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<sup>5</sup> An "MRI" is a non-x-ray technique used to detect joint, tendon, and vertebral disorders. STEDMAN'S MEDICAL DICTIONARY B13 (28th ed. 2006) ("STEDMAN").

<sup>6</sup> A "CT Scan" involves "imaging anatomic information from a cross-sectional plane of the body, each image generated by a computer synthesis of x-ray transmission data obtained in many different directions in a given plane." STEDMAN at 1996.

<sup>7</sup> An "EEG" is "a recording of the potentials on the skull generated by currents emanating spontaneously from nerve cells in the brain. . . . Fluctuations in potential are seen in the form of waves, which correlate well with different neurological conditions and so are used as diagnostic criteria." DORLAND at 600.

Over the next year and a half, Jordan periodically experienced seizures and was treated by various doctors. For example, on April 16, 2005, Jordan was admitted to the Emergency Room at Connecticut Children's Medical Center, because "he was found in crib by mom unresponsive" with his right arm in "tonic flexure." Pet. Ex. 5 at 4. On June 6, 2005, he returned to the Connecticut Children's Medical Center after another tonic-clonic seizure. Pet. Ex. 7 at 1.

On June 10, 2005, Jordan was admitted on referral to Yale New Haven Hospital so that a video EEG could be performed overnight. Pet. Ex. 8 at 7-8. The video EEG and an MRI were performed and the results of both were normal. Pet. Ex. 8 at 15.

On July 13, 2005, Jordan was admitted to Hackensack University Medical Center ("HUMC") after experiencing two seizures and a temperature of 102.7 degrees. Pet. Ex. 10, Vol. 1 at 2.

On July 29, 2005, Jordan was again admitted to HUMC for general tonic-clonic seizure activity.<sup>8</sup> Pet. Ex. 10, Vol. 2 at 697. While there, he had an infectious disease consultation that revealed no causal agent for his fever, but it was speculated that his fever "may be from Hib vaccine day [sic] before." Pet. Ex. 6 at 99-100.

On August 19, 2005, Jordan returned to the HUMC Emergency Room after suffering a two-minute full-body seizure and a fever of 101.6 degrees. Pet. Ex. 10, Vol. 1 at 25. On November 17, 2005, Jordan was taken to the Emergency Room at HUMC after experiencing two seizures and a temperature of 100.5 degrees. Pet. Ex. 10, Vol. 3 at 1066.

On January 26, 2006, Jordan was admitted to the HUMC Emergency Room while experiencing a seizure. Pet. Ex. 10, Vol. 2 at 942. This seizure appears to have lasted from approximately 7:30 a.m. (Pet. Ex. 10, Vol. 2 at 942), until at least 8:32 a.m. *See* Pet. Ex. 10, Vol. 2 at 975 (noting "[f]ull-body twitching"). Jordan was diagnosed as having Status Epilepticus.<sup>9</sup> Pet. Ex. 10, Vol. 2 at 948.

On March 5, 2006, Jordan was taken to the HUMC Emergency Room after experiencing a seizure that lasted for eight minutes, although his temperature on admission was only 98.6 degrees. Pet. Ex. 10, Vol. 2 at 873.

On May 18, 2006, Dr. Daryl De Vivo, M.D., a Neurologist at the Neurological Institute in New York City, was consulted by Jordan's parents. Pet. Ex. 6 at 73-75. Afterwards, Dr. De Vivo opined that he suspected Jordan "may have a genetic mutation in a gene that contributes to epileptogenesis"<sup>10</sup> and suggested genetic screening. Pet. Ex. 6 at 75.

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<sup>8</sup> A "tonic-clonic seizure" is a seizure "consisting of a loss of consciousness and generalized tonic convulsions followed by clonic convulsions." DORLAND at 1688.

<sup>9</sup> "Status Epilepticus" is "any prolonged series of similar seizures without return to full consciousness between them." DORLAND at 1767.

<sup>10</sup> "Epileptogenesis" is "the production or development of epilepsy." DORLAND at 634.

On June 29, 2006, Jordan returned to the HUMC Emergency Room after experiencing a full tonic/clonic seizure that lasted for approximately two minutes, but this seizure was noted as being “different,” because it was without a fever. Pet. Ex. 10, Vol. 2 at 613. A subsequent two-day video EEG taken from June 30-July 1, 2006 was normal. Pet. Ex. 9 at 9-12.

On August 9, 2006, Jordan was evaluated by Dr. Linda Leary, M.D., a Neurologist at Morgan Stanley Children’s Hospital in New York City. Pet. Ex. 6 at 46-50. In reviewing Jordan’s history, Dr. Leary noted that Jordan’s seizure frequency had increased from 1-2 times per month to 1-2 times per week. Pet. Ex. 6 at 47. In addition, his seizures were noted for being variable and occurring with and without fevers. Pet. Ex. 6 at 47. Otherwise, Dr. Leary noted, “[a]ll developmental milestones have been age appropriate.” Pet. Ex. 6 at 46. Given this history, Dr. Leary’s impression was that Jordan’s seizures possibly fit within the spectrum of generalized epilepsy with febrile seizures plus (“GEFS+”).<sup>11</sup> Pet. Ex. 9 at 49. Based on Jordan’s seizure types and normal developmental, Dr. Leary was of the opinion that Jordan was unlikely to have severe myoclonic epilepsy of infancy (“SMEI”),<sup>12</sup> although she observed there was a continuum between the “GEFS+ disorder and that of SMEI with mutations within the SCN1A gene[<sup>13</sup>].” Pet. Ex. 6 at 50.

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<sup>11</sup> “GEFS+” is “a heterogeneous epilepsy syndrome that is characterized by febrile seizures . . . that persist beyond the age of six years, or afebrile seizures exhibiting various phenotypes including generalized epilepsy as well as partial epilepsy.” Gov’t Ex. JJ at 180. GEFS+ has a “variable expression” ranging from just a few febrile seizures to a condition “where there’s no mental development problem but the seizures are a considerable problem.” TR at 63. GEFS+ is more common than, and is considered a less severe disorder than, severe myoclonic epilepsy of infancy, in large part because GEFS+ does not result in developmental delay. TR at 62.

<sup>12</sup> SMEI is a severe seizure disorder that appears during the first year of life. Dravet Syndrome Information Page, NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE, [http://www.ninds.nih.gov/disorders/dravet\\_syndrome/dravet\\_syndrome.htm](http://www.ninds.nih.gov/disorders/dravet_syndrome/dravet_syndrome.htm) (last visited Nov. 19, 2011). Initially, seizures are frequently febrile, *i.e.*, fever-related, though as the disorder progresses other types of seizures occur, including myoclonic seizures. *Id.* Status Epilepticus also may occur. *Id.* The child experiences cognitive impairment, developmental delays in language and motor skills, hyperactivity, and difficulty relating to others, *id.*, although development is initially normal. TR at 61. SMEI is considered to be on a spectrum of disorders with GEFS+ and Borderline Severe Myoclonic Epilepsy of Infancy (“SMEB”). TR at 63, 201. SMEB is similar to SMEI except children with this disorder “lack several key features of SMEI such as myoclonic seizures and generalized spike-wave activity[.]” Pet. Ex. 35 at 844; *see also* TR at 61, 197.

<sup>13</sup> The SCN1A gene codes for the pore region of sodium channels in neurons, *i.e.*, for the portion of the sodium channel responsible for controlling the transport of sodium molecules across cell membranes in the neurons. TR at 434-36; *see also* Gov’t Ex. E at 4. To be specific, it codes for the Na<sub>v</sub>1.1 protein, TR at 436, of the voltage-gated  $\alpha$ 1 subunit of the sodium channel.

On August 15, 2006, Athena Diagnostics, Inc. issued a Diagnostic Report indicating that Jordan had a splice site mutation of the SCN1A gene, a “result . . . consistent with a diagnosis of, or predisposition to developing, SMEI or SMEB[.]” Pet. Ex. 6 at 51. The Report also noted that Jordan’s specific mutation “has not been reported in the literature and/or has not been definitively demonstrated to be associated with SMEI.” Pet. Ex. 6 at 51. Therefore, “[t]he predicted association of this sequence variant with the phenotype<sup>14</sup>] carries some measure of uncertainty.” Pet. Ex. 6 at 51.

On August 29, 2006, Jordan had a genetic evaluation by Dr. Robert Wallerstein, M.D., a Geneticist at HUMC. Pet. Ex. 6 at 18-19. Dr. Wallerstein observed that Jordan has a mutation in the SCN1A gene that has an association with severe myoclonic epilepsy and generalized febrile seizures, but explained that Jordan’s SCN1A mutation did not confirm a diagnosis of SMEI and that Jordan should continue to be monitored. Pet. Ex. 6 at 18. Dr. Wallerstein further observed that children with general febrile seizures who are developmentally normal typically progress to generalized seizures, but children with severe myoclonic epilepsy “typically have regression of milestones during the second year of life.” Pet. Ex. 6 at 18. Given Jordan’s normal development through age two-and-a-half, Dr. Wallerstein was “overall very optimistic.” Pet. Ex. 6 at 18. Dr. Wallerstein recommended determining whether Jordan’s parents had this mutation. Pet. Ex. 6 at 19.

On September 6, 2006, Dr. Wendy Chung, M.D., a Geneticist at Morgan Stanley Children’s Hospital, also conducted a clinical genetic evaluation of Jordan. Pet. Ex. 6 at 43-45. She noted Jordan had a SCN1A splice site mutation that had not previously been reported, and stated:

I believe [Jordan’s SCN1A mutation] is more likely to be associated with the GEFS+ end of the disease spectrum rather than SMEI . . . . In general, many of the splice site mutations that have been previously reported have been somewhat leaky and have either been associated with milder SMEI or GEFS+. The children with the best prognosis tend to have familial mutations which I doubt will be the case for Jordan. Therefore I do not predict that this will be the most benign form of SCN1Aopathy, but will [sic] also not be the worst. In comparison to several other children I follow with mutations in the same gene, those who have had severe epilepsy and associated neurological problems already had more severe developmental delay or myoclonic jerks by Jordan’s age. For that reason, I

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Gov’t Ex. E at 3. As such, “[t]he SCN1A is the major component of [the sodium] voltage-gated channel[.]” TR at 435.

<sup>14</sup> A “phenotype” is “the observable morphological, biochemical, and physiological characteristics of an individual, either in whole or with respect to a single or a few traits, as determined by a combination of the genotype and the environment.” DORLAND at 1431.

believe this is likely to have a better [than] average prognosis for a SCN1A mutation.

Pet. Ex. 6 at 44-45.

On September 24, 2006, Jordan entered into a drug-induced coma after being taken to the HUMC Emergency Room for a seizure lasting an hour and a half. Pet. Ex. 10, Vol. 1 at 348. He was diagnosed as having Status Epilepticus and remained in the hospital until October 3, 2006. Pet. Ex. 10, Vol. 1 at 348.

On October 27, 2006, Athena Diagnostics, Inc. issued a Diagnostic Report stating that Jordan's mother, Nicole, had no "abnormal DNA sequence variants" in her SCN1A gene. Pet. Ex. 6 at 21. On October 31, 2006, Athena Diagnostics, Inc. issued a Diagnostic Report stating that Jordan's father, Frank, had a "DNA sequence variant or combination of variants in the SCN1A gene, whose significance is unknown." Pet. Ex. 6 at 26.

On December 20, 2006, Jordan again was evaluated by Dr. Daryl De Vivo, a Neurologist at the Neurological Institute in New York City. Pet. Ex. 9 at 34-35. He observed that Jordan "has a clinical presentation that is consistent with the GEFS+ phenotype with generalized epilepsy and febrile seizures." Pet. Ex. 9 at 35. Dr. De Vivo's impression was that "[Jordan] has a heterozygous pathogenic mutation in [one] allele of the SCN1A gene and a sequence variation in the other allele that he has inherited from his asymptomatic father. This state of compound heterozygosity is likely causative of the clinical phenotype." Pet. Ex. 9 at 35.

On January 5, 2007, Jordan was admitted to HUMC with a seizure lasting 40 minutes. Pet. Ex. 6 at 37. On January 20, 2007, Jordan was admitted to the HUMC Pediatric Intensive Care Unit for Status Epilepticus. Pet. Ex. 10, Vol. 1 at 161, 194. Jordan suffered another seizure on February 6, 2007 resulting in admittance to the HUMC Emergency Room. Pet. Ex. 10, Vol. 1 at 47.

On March 11, 2007, Jordan returned to the HUMC Emergency Room after suffering a ten-minute seizure at home, and was observed to be "drowsy" with "flaccid" extremities. Pet. Ex. 10, Vol. 3 at 1148.

In a July 11, 2007 Affidavit, Jordan's mother, Nicole, stated:

Since the age of six months Jordan has averaged 1.5 seizures per month. He has had 55 seizures as of June 10, 2007. Jordan has seen several specialists and has been admitted to the hospital for numerous EEG's, MRI's, CAT scans, and metabolic tests in order to identify a causal agent for his seizures.

Pet. Ex. 12 ¶ 28.

Subsequent medical records from the Institute of Neurology and Neurosurgery at St. Barnabas dated June 2, 2009 indicated that Jordan's neurological exams continued to be normal, and recommended that Jordan continue his current medications. Pet. Ex. 58 at 1-2. Those

records also show that, up to that date, Jordan had not had a seizure since February 2009, a period of approximately four months. Pet. Ex. 58 at 1.

## **B. Expert Testimony.**

### **1. The Petitioner's Expert Testimony: Dr. Marcel Kinsbourne.**

Dr. Marcel Kinsbourne graduated from Oxford University Medical School in England in 1955. Pet. Ex. 22 at 1. From there he embarked on a distinguished career in the field of Pediatric Neurology: from 1964 to 1967 he served as a Lecturer at Oxford University; from 1967 to 1974 he was Associate Professor in pediatrics and in neurology at Duke University Medical Center; and from 1974 to 1980 he was Professor of Pediatrics at the University of Toronto Medical School. TR at 9-10; *see also* Pet. Ex. 22 at 2. In 1981, Dr. Kinsbourne left his position at the University of Toronto and became Director of the Behavioral Neurology Department at the Eunice Kennedy Shriver Center, where he focused on research into developmental disabilities. TR at 10-11; Pet. Ex. 22 at 2. In 1995, Dr. Kinsbourne became a Professor of Psychology at the New School University in New York City, where he teaches neuroscience to graduate students. TR at 11; Pet. Ex. 22 at 2. He has published approximately 400 articles and 8 or 9 books. TR at 13; Pet. Ex. 22 at 5-38. Currently, he also serves on the Editorial Board of 12 publications. Pet. Ex. 22 at 3. He is a member of numerous professional societies. Pet. Ex. 22 at 4. And, over the course of his career, Dr. Kinsbourne has won numerous awards, Pet. Ex. 22 at 2, including one awarded by the New School in 2008 for excellence in teaching. TR at 12.

Dr. Kinsbourne's opinion is that a SCN1A "mutation alone appears not to be sufficient to account for the associated epilepsy. . . . [t]here is a gene-environment interaction . . . with an environmental trigger." Pet. Ex. 21 at 5.<sup>15</sup> Dr. Kinsbourne specifically identified the pertussis

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<sup>15</sup> For this conclusion, Dr. Kinsbourne cites: CASPI (2006) (Pet. Ex. 28); *see also id.* at 5 (citing KIMURA (2005) (Pet. Ex. 36) at 425 ("[T]he existence of genetic or environmental factors other than SCN1A mutation may modify SMEI phenotypes . . . different genetic backgrounds and/or environmental factors may critically affect the clinical features of patients with SNC1A mutations[.]")); MULLEY (2005) (Pet. Ex. 38) at 538 ("[O]ther factors, genetic, and/or environmental are contributing [factors] to the more severe SMEI phenotype[.]"); BURGESS (2005) (Pet. Ex. 27) at 53 ("The degree to which these genetically initiated phenotypes are shaped by environmental influences is unclear, but it may be significant."); OTTMAN (2005) (Pet. Ex. 41) at 1530 ("[B]oth gene-gene and gene-environment interactions are likely to be important in many complex diseases[.]"); WALLACE (2005) (Pet. Ex. 45) at 11149 ("The fact that similar mutations cause two different phenotypes implies that other environmental or genetic factors are associated with SMEI."); RHODES (2004) (Pet. Ex. 42) at 11151 ("We would like to speculate that the severe neurological consequences of SMEI are caused by a combination of sodium channel dysfunction . . . with predisposing genetic or developmental factors that lead to a great chance of neuronal injury. In this model, the sodium channel defect creates the initial seizure predisposition, but concomitant excitotoxicity is the direct cause for other neurological features of the disorder[.]"); WALLACE (2005) (Pet. Ex. 45) at 11150 ("Therefore SMEI could be considered a susceptibility factor for both disorders, in which severity is modified by other



component of the DTaP vaccine as an environmental agent, even in its current endotoxin-free acellular formulation,<sup>16</sup> that can invoke a neurological seizure response. Pet. Ex. 21 at 4, 6-9.<sup>17</sup>

In other words, “[t]here is no one-to-one relationship between any of the [disorders on the SMEI spectrum] and any particular variant of SCN1A mutation.” Pet. Ex. 21 at 4.<sup>18</sup> Dr. Kinsbourne found this particularly true for Jordan’s mutation which “was previously unknown or at least undocumented, and the consequences of which were correspondingly quite uncertain.” Pet. Ex. 21 at 4 (referring to Athena Diagnostics, Inc. Report (Pet. Ex. 6 at 51)). For this reason, the fact that parents of children with SCN1A mutations “harbor the same genetic abnormality,” but had no symptoms of a seizure disorder, evidences the necessity of an environmental factor for GEFS+ to manifest.<sup>19</sup>

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environmental and genetic factors . . . predicting the clinical outcome of particular mutations in SCN1A will likely require assessment of other environmental and genetic risk factors[.]”)).

<sup>16</sup> In an April 1, 2010 Post-Hearing Report, Dr. Kinsbourne states that the whole-cell and acellular vaccines contain comparable amounts of pertussis toxin to “stimulate immunity to the wild strain of *Bordetella pertussis*, which causes whooping cough. . . . [I]n the course of the manufacturing of the acellular pertussis vaccine, steps are taken to inactivate pertussis toxin,” but seizures can occur. Pet. Ex. 73 at 1. For this reason, Sanofi Pasteur, the manufacturer of Daptacel and Adacel, “under the heading, Warnings, they warn [sic] that if seizures occurred within three days following the vaccination, ‘careful consideration’ is called for of the risks versus benefits of administering the vaccine again on a future occasion. Indeed, under the heading, Contraindications, under which they list ‘events [that] contraindicate the use of any pertussis containing vaccine,’ they include ‘Encephalopathy within 7 days of a preceding dose’ and ‘uncontrolled epilepsy.’” Pet. Ex. 73 at 1-2 (citing CDC-sponsored Advisory Committee on Immunization Practices (Morbidity and Mortality Weekly Report – MMWR, December 15, 2006) (“Convulsions with or without fever, occurring within 3 days after pediatric DTP/DTaP”)). In support, Dr. Kinsbourne cited CYR (2001) (Pet. Ex. 61) reporting “that toxoided pertussis toxin can spontaneously revert to the active toxic state[.]” Pet. Ex. 73 at 2. In addition, GOMEZ (2007) (Pet. Ex. 66), reports that, even in acellular pertussis vaccine, “‘some residual [pertussis toxin] activity may likely be present because of the limitations of the detoxification processes used.’” Pet. Ex. 73 at 2 (quoting GOMEZ (2007) (Pet. Ex. 66) at 3311).

<sup>17</sup> See also Pet. Ex. 21 at 5 (citing RHODES (2004) (Pet. Ex. 42) at 11151: (“[T]he sodium channel defect creates the initial seizure predisposition, but the concomitant excitotoxicity is the direct cause for other neurological features of the disorder.”); WALLACE (2005) (Pet. Ex. 45) at 19: (“[P]erhaps the sodium channel defect creates the initial seizure predisposition, but concomitant excitotoxicity is the direct cause for other neurological features of SMEI.”)).

<sup>18</sup> Pet. Ex. 21 at 4 (citing HARKIN (2007) (Pet. Ex. 35) at 850 (Table 3); CEULEMANS (2004a) (Pet. Ex. 29); FUJIWARA (2006) (Pet. Ex. 32); OTTMAN (2005) (Pet. Ex. 41) at 1531; TURNBULL (2005) (Pet. Ex. 44)).

<sup>19</sup> Pet. Ex. 21 at 5 (citing ANNESI (2003) (Pet. Ex. 25); GENNARO (2003) (Pet. Ex. 34); NABOUT (2003) (Pet. Ex. 39); FUKUMA (2004) (Pet. Ex. 33); and KIMURA (2005) (Pet. Ex. 36)).

Moreover, if SMEI and GEFS+ were solely was caused by the presence of the SCN1A variant or “purely genetically driven,” the introduction of DTP would not be significant, *i.e.*, there would be “no difference in the probability of seizure onset after DTP[,] as compared to [a] control [group].” Pet. Ex. 21 at 6. The National Childhood Encephalopathy Study (1981) (Pet. Ex. 24) (“NCES”), however, found a “significantly greater incidence of prolonged febrile seizures with onset within three days of DPT vaccination.” Pet. Ex. 21 at 6. Consequently, Dr. Kinsbourne concluded “there is an interaction between a genetic susceptibility factor and the DTP vaccin[e].” Pet. Ex. 21 at 6.

Dr. Kinsbourne proffered two theories as to how the pertussis component of the DTaP vaccine can trigger a seizure. First, the body’s fever reaction “may induce neurochemical changes that lower the seizure threshold[.]” Pet. Ex. 21 at 8 (citing CEULEMANS (2004b) (Pet. Ex. 30) (emphasizing that children should be carefully shielded from fever where possible)). Second, the pertussis toxin either may induce excitotoxicity of neurons leading to their “death” or inability to transmit messages to the brain,<sup>20</sup> or it may attach to a neuron’s membrane interfering with the G protein receptors that control sodium channels.<sup>21</sup> Pet. Ex. 21 at 8; *see also* TR 28.

In other words, “[t]he mutation alone does not predict the form the seizure disorder would take, its severity, the timing of its onset, or even that seizures would necessarily occur. Modifying factors resulting in causation or significant aggravation must exist. Based on the evidence . . . the modifying factors include DTP vaccination.” Pet. Ex. 21 at 8.

Based on the aforementioned, Dr. Kinsbourne concluded:

It is my opinion, to a reasonable degree of medical probability, that the DTaP vaccination, which Jordan Harris received on May 7, 2004, made a significant contribution to the causation of his [GEFS+].

Pet. Ex. 21 at 10.

## **2. The Government’s Expert Testimony: Dr. Max Wiznitzer And Dr. Gerald V. Raymond.**

### **a. Dr. Max Wiznitzer.**

Dr. Wiznitzer graduated from Northwestern University Medical School in 1977. Gov’t Ex. D at 1. Afterwards, he attended a four-year training program at Cincinnati Children’s Hospital, followed by a Child Neurology Fellowship at the University of Pennsylvania and a two-year National Institutes of Health Fellowship studying disorders of higher cortical functioning. TR at 180-81; Gov’t Ex. D at 1-2. He is board certified by the American Board of

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<sup>20</sup> As discussed in RHODES (2004) (Pet. Ex. 42) and WALLACE (2005) (Pet. Ex. 45).

<sup>21</sup> MENKES (2005) (Pet. Ex. 37) at 633.

Pediatrics in Pediatrics and board certified by the American Board of Psychiatry and Neurology both in Neurology, with a Special Competence in Child Neurology, and in Neurodevelopment of Disabilities. TR at 180; Gov't Ex. D at 5. He is also a member of several professional societies, has published about 50 publications, and is a reviewer for a variety of medical journals, including serving on the Editorial Board of LANCET NEUROLOGY and THE JOURNAL OF CHILD NEUROLOGY. TR at 181-83; Gov't Ex. D at 5-6, 12-22. Dr. Wiznitzer is currently employed at the Rainbow Babies and Children's Hospital in Cleveland, Ohio, where he has an active clinical practice treating children with seizure disorders, including several with Dravet's Syndrome or GEFS+. TR at 185; Gov't Ex. D at 3. Dr. Wiznitzer has a special interest in Dravet's Syndrome and attended the first international workshop on Dravet's Syndrome held shortly before the October 8-9, 2009 Evidentiary Hearing in this case. TR at 188-89.

Dr. Wiznitzer's May 25, 2008 Expert Report stated that "[t]here is no evidence that the immunizations administered on 5/7/04 caused or aggravated Jordan Harris's epilepsy." Gov't Ex. C at 3. Rather, Jordan has GEFS+, which "has been shown to have a genetic basis (abnormality of the SCN1A gene) and is not caused by pertussis immunization." Gov't Ex. C at 3. Specifically, "Jordan Harris' testing has shown a *de novo* mutation of the SCN1A gene that affects a splice site, providing 2 proofs for a causal relationship." Gov't Ex. C at 3. From there Dr. Wiznitzer itemized the reasons why Dr. Kinsbourne's opinion was "flawed and has no biological plausibility:" Gov't Ex. C at 3.

1. Dr. Wiznitzer was of the opinion that Jordan's disorder is not properly classified as GEFS+ because Jordan's mutation was not familial, *i.e.*, it was *de novo* and Jordan had no family history of the mutation. Gov't Ex. C at 3, 8. Thus Dr. Wiznitzer thought literature related to GEFS+ was irrelevant in this case. Gov't Ex. C at 3, 8.
2. Dr. Kinsbourne does not offer a full description of the comments in MULLEY (2005) (Pet. Ex. 38). Gov't Ex. C at 4. These authors found that "none of these studies could address [the] question of whether these mutations alter the *in vivo* levels of SCN1A channel expression and processing." Gov't Ex. C at 4 (quoting MULLEY (2005) (Pet. Ex. 38) at 593). Thus, "not enough is known about the *in vivo* effects of the SCN1A mutations to comment on their impact on the clinical phenotype." Gov't Ex. C at 4.
3. "SMEI is genetically determined." Gov't Ex. C at 4. "[L]ater research" by DEPIENNE (2006) (Gov't Ex. I), GENNARO (2006) (Gov't Ex. L), and MORIMOTO (2006) (Gov't Ex. N) provides an explanation for why parents of children that develop SMEI do not have disorders, while the child does, *i.e.*, it is explained by the concept of parental mosaicism.<sup>22</sup> Gov't Ex. C at 4.

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<sup>22</sup> Mosaicism is "the presence in an individual of two or more cell lines that are karyotypically or genotypically distinct and are derived from a single zygote." DORLAND at 1181. In other words, as explained by Dr. Wiznitzer, "the parent has cell populations with and without the SCN1A mutation (so the parent does not have the total burden of the genetic abnormality) and, because the germ cells (single cells – sperm or egg) have the mutation, transmit the full epilepsy syndrome SMEI to the child." Gov't Ex. C at 4.

The articles relied on by Dr. Kinsbourne to support his argument of gene-environment interaction for SMEI, do not support Dr. Kinsbourne's conclusions. Gov't Ex. C at 4-5 (discussing articles by KIMURA (2005) (Pet. Ex. 36), MULLEY (2005) (Pet. Ex. 38), and OTTMAN (2005) (Pet. Ex. 41).

4. NIETO-BARRERA (2000) (Pet. Ex. 40) and YAKOUB (1992) (Pet. Ex. 46) do not evidence a causal relationship between DTP and the onset of SMEI, because "neither study is a true epidemiologic study of SMEI. Secondly, since neither group of authors knew about the proven causal relationship between SMEI and SCN1A gene abnormalities, their discussions about hypothetical seizure mechanisms are outdated and obsolete. Thirdly, the articles discuss DTP, not DTaP, vaccine, the latter having inactivated pertussis toxin. Fourthly, both groups admit that fever is associated with clonic seizures in these children." Gov't Ex. C at 5.

The "NCES finding is not applicable in this case," because Jordan received "DTaP, not DTP, vaccine." Gov't Ex. C at 5. Moreover, Jordan's initial seizure only lasted ten minutes and does not fit the criteria for inclusion in the study. Gov't Ex. C at 5.

5. Dr. Kinsbourne's criticism of BERKOVIC (2006) (Gov't Ex. A) for not referencing NIETO-BARRERA (2000) (Pet. Ex. 40) or NCES or IOM reports is incorrect. Gov't Ex. C at 6. More importantly, Dr. Kinsbourne failed to accurately describe BERKOVIC (2006), wherein the authors state "the role of vaccinations as a significant trigger for encephalopathy is unlikely for several reasons . . . less than half our patients had documented fever with their first seizure, which indicates that fever is not essential . . . individuals with such mutations seem to develop SMEI and SMEB whether or not they are immunized in the first year of life." Gov't Ex. C at 6 (quoting BERKOVIC (2006) (Gov't Ex. A)).
6. Dr. Kinsbourne's theory that "pertussis toxin uncouples the G protein from the receptor, blocking the receptor's normal inhibitory control and allowing glutamate-induced excitotoxicity to have free rein . . . is purely speculative and, in part, dependent on the presence of functional pertussis toxin in DTaP (in which the toxin is inactivated)." Gov't Ex. C at 6. Moreover, none of the references "deal with in vivo neuronal inhibition or excitation." Gov't Ex. C at 7. In addition, "while fever can be associated with the first seizure in children with SMEI . . . it is not necessary for seizure occurrence[.]" Gov't Ex. C at 7 (citing CUELMANS (2004c) (Gov't Ex. H), OHKI (1997) (Gov't Ex. Q), OGUNI (2001) (Gov't Ex. P)). Moreover, "[t]he source of the temperature elevation is not important[.]" Gov't Ex. C at 7 (citing OGUNI (2001) (Gov't Ex. P)). Thus, "children with SMEI (and its associated SCN1A mutation) always manifest the disorder since (1) fever is not necessary for the occurrence of the seizure and (2) the mild rise in body temperature associated with seizure occurrence cannot be avoided . . . and will occur in every child." Gov't Ex. C at 7-8.

Therefore, Dr. Wiznitzer's opinion was:

1. While SCN1A mutations can be *associated* with different seizure disorders, there is no evidence that "environmental factors" such as pertussis vaccination "have a substantial contributory causative factor". Mosaicism explains the occurrence of SMEI in a child and less severe seizure disorder in the parent.
2. Immunizations are not necessary or causal factors and their avoidance does not alter the natural history of SMEI (per Dr. Kinsbourne's discussion). Therefore, DTP or DTaP are not factors in the epilepsy's causation, and there is no evidence of gene-environment interaction in this case.
3. Dr. Kinsbourne's hypothesis on the action of pertussis toxin on neurons is not a biologically plausible mechanism of injury in children with SMEI.
4. While fever can be associated with seizures in SMEI and GEFS+, it is not a "mechanism of injury" but, rather, a factor that does not alter the evolution of the epilepsy or influence the adverse cognitive outcome.

Gov't Ex. C at 9 (emphasis added).

**b. Dr. Gerald V. Raymond.**

Dr. Raymond graduated from the University of Connecticut Medical School in 1984. Gov't Ex. F at 1. Thereafter, he was an intern and Junior Assistant Resident in Pediatrics at Johns Hopkins Hospital and a Resident in Neurology at Massachusetts General Hospital. Gov't Ex. F at 1. He was then awarded research fellowships in Developmental Neuropathy at Universite Catholique de Louvain in Brussels, Belgium, and in Genetics and Teratology at Massachusetts General Hospital. Gov't Ex. F at 1. In addition, Dr. Raymond is board certified by the American Board of Psychiatry and Neurology in Neurology, with a Special Qualification in Child Neurology, and board certified by American Board of Medical Genetics in Clinical Genetics. Gov't Ex. F at 10; TR at 394. Dr. Raymond testified that he is among the four or five physicians in the United States with dual certification in Neurology and Genetics. TR at 394. In addition, Dr. Raymond is a reviewer for a number of publications, a member of several professional societies, regularly gives lectures on neurogenetics, has published approximately 70 articles in peer-reviewed journals, and has authored more than a dozen chapters in books. TR at 397-98. Currently, he is employed as the Director of Neurogenetics at the Kennedy Krieger Institute in Baltimore, Maryland and is an Associate Professor of Neurology at Johns Hopkins Medical School. TR at 391-92. At Kennedy Krieger, approximately 75% of Dr. Raymond's time is devoted to clinical research. TR at 392. The remainder of his time is mostly spent on assisting in the diagnosis and treatment of patients, and he estimates that he has consulted with two or three patients who have evidenced Dravet's Syndrome. TR at 392, 395-96. At Johns Hopkins he teaches both neurology and genetics. TR at 393.

Dr. Raymond acknowledged that SCN1A mutations have been associated with a variety of neurological conditions, but stated that this is not unusual for genetic disorders. Gov't Ex. E

at 5. In this regard, “[i]t is *not necessary* to invoke environmental or even other genetic factors in such varied phenotypic expression. Rather the type and position of the mutation with subsequent effect on the function of the protein is sufficient to have very divergent conditions.” Gov’t Ex. E at 6 (emphasis added). For this reason, the spectrum of disorders associated with the SCN1A mutation was explained by non-environmental factors. Gov’t Ex. E at 6.

In Jordan’s case, the fact that his mutation is a splice site mutation that arose *de novo* in a highly conserved region of the human genome are all important factors that are viewed as highly likely to be disease-causing. Gov’t Ex. E at 5; *see also* TR at 450-54 (discussing Jordan’s mutation). In fact, the presence of these factors would lead to a prediction of a more severe disease, such as SMEI, a prediction consistent with that made by Athena Diagnostics. Gov’t Ex. E at 5. At the Evidentiary Hearing, Dr. Raymond opined that the reason the outcome was not actually as severe as predicted is that the mutation was “leaky,” *i.e.*, that some messenger RNA<sup>23</sup> is being formed when one would expect that no messenger RNA would be formed. TR at 532-33, 536-38; *see also* Gov’t Ex. E at 5 (offering the possibility of a leaky mutation or mosaicism for the less severe outcome).

Like Dr. Wiznitzer, Dr. Raymond also critiques some of the empirical studies cited by Dr. Kinsbourne to establish a causal relationship. For example, as to YAKOUB (1992) (Pet. Ex. 46), the authors do not state which vaccinations preceded severe epilepsies, nor do they describe the vaccinations as “triggering event[s].” Gov’t Ex. E at 6. As to NIETO-BARRERA (2000) (Pet. Ex. 40), Dr. Raymond notes methodological problems arising from its retrospective nature and lack of information as to whether the patients had an SCN1A mutation. Gov’t Ex. E at 6. In addition, Dr. Raymond noted that NIETO-BARRERA undermines Dr. Kinsbourne’s view that the epilepsy-causing effect of the pertussis vaccine is unlikely to be due to fever alone, because NIETO-BARRERA shows that patients had a variety of illnesses before their first seizure, making it apparent that a mild fever from any source can trigger a seizure. Gov’t Ex. E at 6-7. Dr. Raymond adds, however, that a fever is not a necessary event. Gov’t Ex. E at 7. In fact, Dr. Raymond states that “individuals with [GEFS+] go on to have a variety of seizures unrelated to fever.” Gov’t Ex. E at 7. Dr. Raymond also disputes Dr. Kinsbourne’s critique of BERKOVIC (2006) (Gov’t Ex. A), because Dr. Kinsbourne failed to “acknowledge the substantial literature which calls into question the conclusions of the NCES” study on which Dr. Kinsbourne relied. Gov’t Ex. E at 7.

In addition, Dr. Raymond challenged Dr. Kinsbourne’s G protein theory. Gov’t Ex. E at 7. Although G-proteins can be affected by pertussis toxin, Dr. Kinsbourne cites, and Dr. Raymond found, no literature supporting a specific theory of “direct interaction between G-protein coupled receptors and voltage-gated sodium channels[.]” Gov’t Ex. E at 7.

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<sup>23</sup> “Messenger RNA” are “RNA molecules . . . that serve as templates for protein synthesis (translation).” DORLAND at 1650. In other words, the messenger RNA is ultimately translated into the production of proteins. TR at 408. A splice site mutation “alters the subsequent assembly of a messenger RNA.” TR at 531.

Furthermore, Dr. Raymond declined to adopt Dr. Kinsbourne's argument regarding the toxoiding process,<sup>24</sup> because:

There has been no evidence in the medical literature of an environmental modifier or any interaction between mutations in SCN1A and immunizations. In addition, there is no evidence that any of the diseases or toxins that the immunizations protect against interact with SCN1A.

Gov't Ex. E at 7.

Dr. Raymond's opinion is "to a reasonable degree of medical certainty . . . Jordan . . . has [GEFS+] . . . secondary to a mutation in his SCN1A gene. This is the sole cause of his epilepsy condition. It was not caused nor exacerbated by any of the immunizations that he received." Gov't Ex. E at 8.

## **II. PROCEDURAL HISTORY.**

On January 24, 2007, Jordan's father, Frank Harris, filed a petition in the United States Court of Federal Claims seeking compensation under the National Vaccine Injury Compensation Act for injury resulting from the administration of the DTaP vaccine. The case was assigned to Special Master Christian J. Moran ("the Special Master").

On May 18, 2007, Petitioner filed a compact disc (CD) of Jordan's medical records. Pet. Exs. 1-11. On July 12, 2007, Petitioner filed an Amended Petition containing a more thorough recitation of Jordan's medical history and an explanation why Jordan's SCN1A mutation should not prevent recovery. On July 23, 2007, Petitioner filed a CD of medical literature and a scientific reference manual. Pet. Exs. 14-16.

On August 20, 2007, the Government filed a Report, pursuant to Rule 4(c), together with a medical article, Samuel F. Berkovic et al., *De-novo mutations of the sodium channel gene SCN1A in alleged vaccine encephalopathy: a retrospective study*, 5 LANCET NEUROLOGY 465-66, 488-92 (2006). Gov't Ex. A.

On August 28, 2007, Petitioner filed additional medical records. Pet. Exs. 17-20.

On August 30, 2007, the Government filed the webpage cited in footnote 2 of its Rule 4(c) Report, filed on August 20, 2007. Gov't Ex. B.

On February 6, 2008, Petitioner filed the Expert Report and Curriculum Vitae of Dr. Marcel Kinsbourne, M.D. Pet. Exs. 21-22. On February 25, 2008, Petitioner filed a CD

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<sup>24</sup> A "toxoid" is "a modified or inactivated bacterial exotoxin that has lost toxicity but retains the properties of combining with, or stimulating the formation of, antitoxin." DORLAND at 1943. Toxoiding is the process by which the toxicity is removed. See TR at 23-27 (Dr. Kinsbourne discussing toxoids and the toxoiding process).

indexing supporting relevant medical literature. Pet. Exs. 23-46. On April 9 and April 10, 2008, Petitioner filed additional and updated medical records. Pet. Exs. 47-48.

On June 3, 2008, the Government filed the Expert Reports and Curricula Vitae of Dr. Max Wiznitzer, Gov't Exs. C-D, and Dr. Gerald Raymond, Gov't Exs. E-F, together with medical literature. Gov't Exs. G-R. On June 19, 2008, additional medical literature was filed by the Government. Gov't Exs. S-Z, AA-EE.

On June 24, 2008, Petitioner filed a Motion To Transfer And/Or Consolidate this case with *Snyder v. Sec'y of HHS*, No. 07-59V, because the issues presented in both cases were similar, the same attorneys represented the parties, and both parties had the same expert witnesses. On June 27, 2008, the Government filed a Motion in Opposition. On July 3, 2008, then Chief Special Master Golkiewicz granted Petitioner's Motion To Transfer and Special Master Moran was assigned both cases. *See Snyder v. Sec'y of HHS*, No. 07-59V, ECF No. 49.

On July 24, 2008, Petitioner filed a CD of updated medical records. Pet. Ex. 49. On December 15, 2008, Petitioner filed an additional CD containing additional medical records. Pet. Exs. 50-52.

On December 30, 2008, Petitioner filed a Motion To Transfer And/Or Consolidate with: *Hammitt v. Sec'y of HHS*, No. 07-170V; *Stone v. Sec'y of HHS*, No. 04-1041V; and *Santini v. Sec'y of HHS*, No. 06-725V. In response, the Government filed a Renewed Opposition to Petitioner's Second Motion To Transfer And/Or Consolidate. On January 9, 2008, then Chief Special Master Golkiewicz denied Petitioner's Second Motion To Transfer And/Or Consolidate.

On January 13, 2009, Petitioner filed a Motion For A Ruling On Reasonable Basis To Continue. On January 16, 2009, the Special Master granted the Petitioner's Motion To Continue.

On March 18, 2009, Petitioner filed the Supplemental Medical Expert Report of Dr. Kinsbourne. Pet. Ex. 53.

On April 24, 2009, the Government filed a Supplemental Expert Report of Dr. Raymond. Gov't Ex. GG. In addition, the Government requested permission to file the ANTONARAKIS (2001) article referenced in the Government's experts' reports. Gov't Ex. FF. The Government also filed a table of the medical literature they had filed in *Snyder v. Sec'y of HHS*, No. 07-59V and *Harris v. Sec'y of HHS*, No. 07-60V. Gov't Ex. HH.

On September 1, 2009, Petitioner filed medical literature in support of Dr. Kinsbourne's February 6, 2008 Expert Report. Pet. Exs. 54-56. On September 8, 2009 and September 15, 2009, Petitioner filed additional updated medical records. Pet. Exs. 57, 58.

On September 30, 2009, the Government filed additional medical literature. Gov't Exs. JJ-KK.



On October 5, 2009, the Government filed a Trial Exhibit containing a PowerPoint presentation to be used by Dr. Raymond during his direct testimony in the Evidentiary Hearing. Gov't Trial Ex. 1.

On October 8-9, 2009, the Special Master conducted an evidentiary hearing in Boston, Massachusetts in regards to both *Harris v. Sec'y of HHS*, No. 07-60V, and *Snyder v. Sec'y of HHS*, No. 07-59V. *See Snyder v. Sec'y of HHS*, No. 07-59V, ECF Nos. 91, 93. During the Evidentiary Hearing the Special Master heard testimony from the Petitioner's expert, Dr. Kinsbourne, and the Government's experts, Dr. Wiznitzer and Dr. Raymond. TR at 1-594.

On October 13, 2009, the Government filed additional medical literature. Gov't Amended Ex. HH; Gov't Exs. LL-SS.

On November 4, 2009, Petitioner filed additional medical literature. Pet. Exs. 59-72.

On December 18, 2009, the Government filed the Additional Expert Reports of Dr. Wiznitzer and Dr. Raymond. Gov't Exs. TT-UU.

On April 5, 2010, Petitioner filed an Additional Expert Report by Dr. Kinsbourne, along with additional medical literature. Pet. Ex. 73.

On May 24, 2010, the Government filed a Motion For Leave To File Medical Article. Gov't Ex. VV. On June 4, 2010, Petitioner filed a Motion To Strike The Government's Exhibit VV from the record. On June 10, 2010, the Special Master granted the Government's May 24, 2010 Motion.

On July 19, 2010, Petitioner filed a Supplemental Expert Report of Dr. Kinsbourne, together with additional supporting medical literature. Pet. Ex. 74.

On September 24, 2010, the Government filed additional medical literature. Gov't Ex. WW.

On May 27, 2011, the Special Master issued a decision denying compensation to Petitioner, because "[t]he evidence overwhelmingly favors a finding that Jordan's epilepsy was caused solely by a mutation in the SCN1A gene." *Harris v. Sec'y of HHS*, No. 07-60V, 2011 WL 2446321 \*35 (Fed. Cl. Spec. Mstr. May 27, 2011).

On June 27, 2011, Petitioner filed a Motion For Review of the Special Master's May 27, 2011 Decision. The same day, Petitioner's Motion For Review was assigned to the Honorable Judge Lynn J. Bush. On July 1, 2011, the case was transferred to the undersigned judge, pursuant to RCFC 40.1(b).

On July 27, 2011, the Government filed a Memorandum In Response to Petitioner's Motion For Review of the Special Master's May 27, 2011 Decision.

### III. DISCUSSION.

#### A. Jurisdiction And Standard Of Review.

Section 300aa-12(e) of the Vaccine Act authorizes the United States Court of Federal Claims to review the decision of a special master. *See* 42 U.S.C. § 300aa-12(e)(2) (“The United States Court of Federal Claims shall have jurisdiction[.]”). The same section also authorizes the court, in reviewing a decision of a special master, to (1) “uphold findings of fact and conclusion of law,” (2) “set aside any findings of fact or conclusion of law . . . found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law,” or (3) “remand the petition to the special master for further action in accordance with the court’s direction.” *Id.*

Findings of fact by a special master are to be reviewed under an “arbitrary and capricious standard;” legal conclusions are reviewed under a “not in accordance with law standard;” and discretionary rulings are reviewed for “abuse of discretion.” *Saunders v. Sec’y of HHS*, 25 F.3d 1031, 1033 (Fed. Cir. 1994) (internal quotations omitted). The United States Court of Appeals for the Federal Circuit has held that “[i]f the special master has considered the relevant evidence of record, drawn plausible inferences and articulated a rational basis for the decision, reversible error will be extremely difficult to demonstrate.” *Hines v. Sec’y of HHS*, 940 F.2d 1518, 1528 (Fed. Cir. 1991). It is not the role of a court “to reweigh the factual evidence, or to assess whether the Special Master correctly evaluated the evidence.” *Lampe v. Sec’y of HHS*, 219 F.3d 1357, 1360 (Fed. Cir. 2000) (internal quotations omitted); *see also Porter v. Sec’y of HHS*, 2010-5162, \_\_\_ F.3d \_\_\_, 2011 WL 5840315 (Fed. Cir. Nov. 22, 2011).

#### B. The Special Master’s May 27, 2011 Decision.

On May 27, 2011, the Special Master issued an Entitlement Decision. *Harris*, 2011 WL 2446321. The decision began by evaluating the role of an identified SCN1A gene mutation in causing Jordan’s GEFS+ disorder in this case. *Id.* at \*11. The Special Master concluded that this issue was the “key dispute” in the case. *Id.* In this regard, the Special Master “assume[d] that Mr. Harris has met his burden of establishing that the [DTaP] vaccination can affect seizure disorders.” *Id.*

After a lengthy discussion, Special Master Moran concluded that “[t]he evidence overwhelmingly favors a finding that Jordan’s epilepsy was caused solely by a mutation in the SCN1A gene.” *Id.* at \*35. Accordingly, the Special Master determined that Petitioner was “not entitled to compensation” under the Vaccine Act. *Id.*

To support the conclusion that the SCN1A mutation was the sole cause of Jordan’s GEFS+ disorder, the Special Master relied on the testimony of Dr. Raymond, whom the Special Master considered “the most qualified expert to express an opinion.” *Id.* at \*13. In light of the testimony of Dr. Raymond, it was particularly important that Jordan’s mutation was a splice site mutation that arose *de novo* in a conserved region of the human genome.<sup>25</sup> *Id.* at \*14.

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<sup>25</sup> A *de novo* mutation is significant, because it “is much more likely to present a severe disease[.]” *Id.* at \*14 (citing MULLEY (2005) (Pet. Ex. 38)). “Conserved regions” are genetic

Furthermore, a precedent case reported in an article by KUMAKURA (2009) (Gov't Ex. JJ) involved a child with the same SCN1A mutation and a similar clinical presentation, indicating that "this particular mutation tends to control the person's development." *Id.* at \*15 (citing TR at 213-15 (Dr. Wiznitzer); TR at 450, 560-61 (Dr. Raymond)). The Special Master found the rebuttal argument of Dr. Kinsbourne that such databases are biased to over-reporting cases with severe diseases unpersuasive. *Id.*

The Special Master also rejected the Petitioner's argument that numerous articles indicate that an environmental trigger is also necessary to cause symptoms. *Id.* at \*16. Instead, the Special Master found that a "more accurate generalization is that some authors have suggested that environmental factors may influence how a genetic mutation manifests clinically." *Id.* The Special Master then discussed each of several articles in turn, determining that they do not support the Petitioner's position. *Id.* at \*\*16-20 (discussing articles by BERKOVIC (2006) (Gov't Ex. A); SELL (2006) (Pet. Ex. 43); NIETO-BARRERA (2000) (Pet. Ex. 40); RHODES (2004) (Pet. Ex. 42); WALLACE (2005) (Pet. Ex. 45); BURGESS (2005) (Pet. Ex. 27); KIMURA (2005) (Pet. Ex. 36); GAMBARDILLA (2009) (Pet. Ex. 54); DEPIENNE (2008) (Pet. Ex. 56); LOSSIN (2009) (Pet. Ex. 55); CLAES (2009) (Gov't Ex. KK); and YAKOUB (1992) (Pet. Ex. 46)). In sum, the Special Master determined that "Mr. Harris should have presented persuasive evidence that environmental factors influence the expression of the SCN1A gene[,] but he did not. *Id.* at \*20.

Moreover, the Special Master found the testimony of Dr. Kinsbourne on the subject of SCN1A unpersuasive. *Id.* at \*20-21. In particular, the Special Master faulted Dr. Kinsbourne for his lack of experience treating people with SCN1A defects, his lack of practical clinical experience since he essentially stopped practicing pediatric neurology in 1981, and his current position working as a professor teaching psychology to non-medical students. *Id.* at \*21.

Dr. Kinsbourne's experience was contrasted unfavorably with the Government's experts' experience in studying neurological problems associated with genetic abnormalities, and their subsequent opinions that the SCN1A gene was the cause of Jordan's epilepsy. *Id.* at \*\*21-22 (citing TR at 185-86, 209-10 (Dr. Wiznitzer); TR at 395-96 (Dr. Raymond)). The Special Master found that their opinions were supported by the medical literature. *Id.* at \*22 (discussing articles by BERKOVIC (2006) (Gov't Ex. A), CLAES (2009) (Gov't Ex. KK), and CEULEMANS (2004a) (Pet. Ex. 29)). In particular, the Special Master was persuaded by the conclusions by the authors of MCINTOSH (2010) (Gov't Ex. VV) that the DTaP vaccine does not affect the severity of the outcome in patients that have both Dravet's Syndrome and an SCN1A mutation. *Id.* at \*\*22-23.

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sequences that appear in other species and are thought to be important "because their continued presence suggests that a species could not function without the particular genetic sequence." *Id.* (citing TR at 430, 444-45, 507, 556-58; DEPIENNE (2008) (Pet. Ex. 56), MULLEY (2005) (Pet. Ex. 38)). Finally, a mutation at a splice site "is a change in the sequence of amino acids that control how DNA is transcribed into messenger RNA," part of the process of which involves slicing DNA into smaller portions. *Id.* (citing TR at 407, 410-12; Gov't Trial Ex. A at 8-9). Thus splice site mutations "tend[] to indicate a disease." *Id.* (citing TR at 451-53, 530-31, 557).

Finally, the Special Master found that the medical records of Jordan's treating doctors support the finding that Jordan's SCN1A mutation was the sole cause of his disorder. *Id.* at \*23. The Special Master found the reports of Dr. Chung and Dr. Wallerstein most informative because both treated Jordan after the mutation was discovered and because both are geneticists. *Id.* In this regard, both doctors found the SCN1A mutation predicted a seizure disorder and neither suggested that the DTaP vaccine affected Jordan's outcome, though at least Dr. Chung was aware of the DTaP vaccination's temporal association with the initial seizure. *Id.* It was also noted that Dr. Chung predicted that Jordan's disorder would more likely be GEFS+ than SMEI. *Id.* (citing Pet. Ex. 6 at 44-45). Finally, other medical records pointed to by the Petitioner as drawing a link between the vaccine and seizure do not indicate that these treating physicians drew a causal link, and instead indicate that these doctors recognized a temporal association. *Id.* at \*23 n.22 (citing Pet. Ex. 4 at 2, 41; Pet. Ex. 7 at 46-47).

After assessing this evidence, the Special Master concluded that "[t]he finding that the SCN1A mutation was solely responsible for causing Jordan's epilepsy resolves this case. This finding necessarily implies that the DTaP vaccine *did not affect* Jordan's epilepsy." *Id.* at \*24 (emphasis added).

Having addressed the role of the SCN1A mutation, the Special Master next turned to the Petitioner's evidence regarding DTaP vaccine and seizure disorders. *Id.* In this regard, the Special Master elaborated that even if the SCN1A mutation was not the sole cause of the disorder, the Petitioner would still need to establish by a preponderance of the evidence a medical theory causally connecting a significantly worsened condition to the vaccine. *Id.* (citing *Loving v. Sec'y of HHS*, 86 Fed. Cl. 135, 144 (2009)). To meet his burden, the Petitioner put forward two medical theories that the Special Master found "lacked clarity." *Id.*

The Special Master first addressed Petitioner's argument that DTaP vaccine affects cells in the central nervous system to make seizures more likely by examining each of "three discrete propositions" contained in the theory. *Id.* at \*25. The first proposition is that the lack of complete toxoiding leaves some dangerous pertussis toxin in the acellular pertussis vaccine. *Id.* (citing TR at 25-27, 154-55). The Special Master thought the discussion of this issue would be better informed by someone with pharmacology expertise. *Id.* He also thought it was problematic that there was no testimony on the articles that supported Dr. Kinsbourne's opinion. *Id.* In light of these problems, the Special Master found that the evidence on this point "was not presented well" and thus thought it made "little sense to address whether the toxoiding process completely inactivates all pertussis toxin." *Id.* at \*26.

The second proposition is that the pertussis toxin can cross the blood-brain barrier, which Dr. Kinsbourne argued could happen when a fever increases the permeability of the barrier. *Id.* The Special Master found that the evidence in this case "seems to be about the same as the evidence in *Moberly*["] because Petitioner did not present any evidence "shor[ing] up" the argument, but "just [presented] Dr. Kinsbourne's unsupported assertion[.]" *Id.*

The third and final proposition is that the pertussis toxin damages the nervous system. In this regard, the Special Master addressed what he viewed as three distinct theories put forward by Dr. Kinsbourne, and faulted Dr. Kinsbourne for changing his reasoning. *See id.* Initially, Dr.

Kinsbourne put forward a theory “that pertussis toxin ‘uncouples the G protein receptors . . . [that] have inhibitory control over voltage gated sodium channels.’” *Id.* at \*27 (quoting Pet. Ex. 21 at 10). Then, at the Evidentiary Hearing, Dr. Kinsbourne asserted a different theory “that the SCN1A mutation affects neurons that inhibit seizures and that pertussis’s effect on G proteins also affects inhibitory neurons” and thus the two influences converge to affect Jordan’s disorder. *Id.* (citing TR at 33-34). In support of this theory, Dr. Kinsbourne offered articles by CATTERALL (2008) (Pet. Ex. 59) and THALMANN (1988) (Pet. Ex. 64). *Id.* When Dr. Wiznitzer rebutted the notion that the THALMANN article discussed sodium channels, Dr. Kinsbourne denied that he had asserted the article concerned sodium channels and introduced his third theory “that the THALMANN article showed that G-proteins control inhibitory neurons with a potassium channel[.]”<sup>26</sup> *Id.* (citing TR at 375-76).

The Special Master found evaluating Dr. Kinsbourne’s opinion “difficult” in light of Dr. Kinsbourne putting forward what the Special Master characterized as three distinct theories. *Id.* The Special Master found that the Petitioner did not establish the reliability of the first two theories. *Id.* As to the third theory, the Special Master thought it “would not be wise” to evaluate the theory on the basis of the record in this case. *Id.*

Finally, the Special Master finished by addressing the Petitioner’s argument on the effect of pertussis toxin on neurons by examining a study done by the English government titled the National Childhood Encephalopathy Study (“NCES”) (Pet. Ex. 24). *Id.* at \*28. This study found that there was a greater incidence of acute neurological incidents within a month of receiving the DTP vaccine, *i.e.*, the whole-cell version of the pertussis vaccine. *Id.* The Special Master found using a study about the whole-cell pertussis vaccine to draw conclusions concerning the acellular pertussis vaccine “problematic.” *Id.* To begin with, only about as third as many reactions have been reported with the acellular vaccine, leading Dr. Wiznitzer to claim that the resulting incidence rate would approximately match the background rate, a claim disputed by Dr. Kinsbourne. *Id.* (citing TR at 231-36, 334-36 (Dr. Wiznitzer); TR at 355 (Dr. Kinsbourne)). Second, other special masters have rejected similar extrapolations in several cases. *Id.* (citing *Stone v. Sec’y of HHS*, No. 04-1041V, 2010 WL 1848220, at \*10 n.15 (Fed. Cl. Spec. Mstr. Apr. 15, 2010) *remanded on other grounds* 95 Fed. Cl. 233 (2010); *Teller v. Sec’y of HHS*, No. 06-804V, 2009 WL 255622, at \*4 n.9 (Fed. Cl. Spec. Mstr. Jan. 13, 2009); *Simon v. Sec’y of HHS*, No. 05-941V, 2007 WL 1772062, at \*7 (Fed. Cl. Spec. Mstr. June 1 2007)). The Special Master also found that Dr. Wiznitzer was not better qualified to interpret the NCES study than Dr. Kinsbourne. *Id.* at \*29. Since the evidence “clearly and convincingly” shows that Jordan would have been the same due to the SCN1A mutation, the Special Master declined to draw any conclusions about applying studies on whole-cell pertussis vaccine to the acellular pertussis vaccine. *Id.*

The Special Master next turned to the Petitioner’s second theory, *i.e.*, that the pertussis vaccine caused a fever that then caused the seizure that then substantially contributed to the GEFS+. *Id.* As to this argument, the Special Master found that “[a] preponderance of the

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<sup>26</sup> As the Special Master noted, “[n]eurons contain different types of channels, including sodium channels, potassium channels, and calcium channels.” *Id.* at \*27 n.26 (citing TR at 241; (Dr. Wiznitzer); TR at 376 (Dr. Kinsbourne); TR at 562 (Dr. Raymond)).

evidence supports finding that DTaP vaccine can cause fevers and fevers can cause seizures.” *Id.* The critical issue is then whether the DTaP vaccine, even if it caused the first seizure, affected Jordan’s ultimate outcome. *Id.*

The Special Master’s discussion of this issue focused on two different mice studies discussed in two different articles, one by OAKLEY (2008) (Gov’t Ex. II) and one by YU (2006) (Gov’t Ex. WW), in which the equivalent of the SCN1A gene had been knocked out of the mice to determine if they would develop seizures. *Id.* at \*\*29-32. The dispute over the articles concerned whether the mice were heated before they began to experience spontaneous seizures. *Id.* at \*\*30-31. Petitioner argued that the mice in the YU article must have experienced elevated temperatures after having surgically implanted electrodes removed. *Id.* at \*31 (citing Pet. Resp. at 2). The Special Master found this interpretation “strained” and ultimately unpersuasive, in part because the YU researchers “did not report any temperature measurements after surgery.” *Id.* at \*32. Given this finding, the Special Master found that the experiment showed that the mice would develop seizures regardless of whether they had been heated, and thus “[h]umans with [an SCN1A] mutation do not need to have a fever to have a seizure.” *Id.* Moreover, the Special Master noted that “[a]lthough the first seizure in many cases of SMEI is a seizure associated with a fever, all cases of SMEI do not start that way.” *Id.* In sum, with regard to the Petitioner’s fever-based theory, the Special Master found that “[t]he DTaP vaccine triggered a fever and the fever triggered a seizure. But, Jordan would have had a seizure even if he never had a fever. The seizure was an inevitable result of the SCN1A mutation. The fever did not affect Jordan’s development.” *Id.*

Lastly, the Special Master turned to the question of whether Petitioner had established that Jordan suffered an injury lasting more than six months, an inquiry the Special Master called an “alternative method for analyzing Jordan’s case[.]” *Id.*

The Special Master began by pointing out that Dr. Kinsbourne refused to offer an opinion as to how Jordan would have been different but for the vaccination. *Id.* at \*33 (citing TR at 118, 172). Furthermore, the Special Master found Dr. Kinsbourne’s opinion that persons with the defect might suffer a disorder lower on the SMEI spectrum “inherently speculative.” *Id.* Moreover, it overlooks the fact that Jordan does not have SMEI, but GEFS+, a less devastating condition. *Id.* In contrast, the Special Master found that the Government’s experts had no such uncertainty in their opinions that the vaccine did not alter Jordan’s outcome. *Id.* (citing TR at 222-23, 226, 346, 349-50 (Dr. Wiznitzer); TR at 455, 474, 523, 546 (Dr. Raymond)). This testimony the Special Master found “compelling.” *Id.*

Moreover, the Special Master pointed out that the experts did not assert that the fever alone caused lasting consequences. *Id.* at \*34. In particular, Dr. Kinsbourne did not say whether the fever was necessary to trigger the seizure disorder. *Id.* (citing TR at 108). In addition, Dr. Kinsbourne was not of the opinion that Jordan’s relatively early onset of seizures made his disorder more severe. *Id.* In contrast, the Government’s experts “were more emphatic” in rejecting the idea that the fever altered the outcome, including the notions that the initial fever would lower the seizure threshold or that the length and type of seizure affected the ultimate outcome. *Id.* (citing TR at 237, 306, 256-57 (Dr. Wiznitzer); TR at 460, 518-19 (Dr. Raymond)).

In light of this evidence, the Special Master found that the DTaP vaccine did not affect Jordan's epilepsy for more than six months and instead the evidence is more consistent with the notion that the outcome is the same as it would have been but for the vaccine. *Id.* This finding was "derive[d] from the finding that the genetic mutation was the sole cause of Jordan's epilepsy." *Id.*

**C. Petitioner Has Established Entitlement To Compensation Under The Vaccine Act.**

**1. Petitioner Has Demonstrated, By A Preponderance Of The Evidence, That His GEFS+ Syndrome Was Caused-In-Fact By The DTaP Vaccine.**

The United States Court of Appeals for the Federal Circuit held in *Althen v. Sec'y of HHS*, 418 F.3d 1274 (Fed. Cir. 2005), that a claim under the Vaccine Act for injury, based on causation-in-fact, requires the petitioner to establish three elements by a preponderance of evidence:

(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between [the] vaccination and injury.

*Id.* at 1278; *see also id.* at 1280 (holding that none of these elements are required to be established by "scientific certainty," but only by a preponderance of evidence); *see also Capizzano v. Sec'y of HHS*, 440 F.3d 1317, 1324 (Fed. Cir. 2006) (same).

Therefore, to show causation, a petitioner need not show that the vaccine was the *only* cause of his injury, but only that it was a "substantial factor" in bringing about the harm, and that the harm would not have occurred but for the action." *Shyface v. Sec'y of HHS*, 165 F.3d 1344, 1352 (Fed. Cir. 1999) (quoting RESTATEMENT (SECOND) OF TORTS § 431 (1965)). Evidence proffered to establish one element of the *Althen* test also may establish another element. *See Capizzano*, 440 F.3d at 1326.

In this case, the Special Master assumed or conceded in the Decision Denying Compensation that Petitioner satisfied his burden to establish causation-in-fact under *Althen*, but described this finding as "generous." *See Harris*, 2011 WL 2446321 at \*11. Later in the Decision, however, the Special Master revisited the alternative medical theories posited by Dr. Kinsbourne. *Id.* at \*\*24-34. The Special Master characterized Dr. Kinsbourne's opinion as to "how pertussis toxin affects neurons" as "difficult" to evaluate, because his explanations seemed to change at different junctures during the litigation. *Id.* at \*27. Nevertheless, the Special Master found "there were shortcomings in the parties' presentations" as to "whether acellular pertussis vaccine can damage brain cells[.]" *Id.* at \*29. Accordingly, the Special Master declined to make a conclusion about this theory. *Id.*

Next, the Special Master turned to the medical theory that “the pertussis toxin in Jordan’s DTaP vaccine caused the fever that caused the seizure activity that led to severe epilepsy.” *Id.* Here, the Special Master found that “[a] preponderance of evidence supports finding that DTaP vaccine can cause fevers and fevers can cause seizures.” *Id.* After a detailed discussion about two medical articles reporting on an experiment on mice resulting in a mixed record and a “divergent understanding of the experiments,” the Special Master proceeded to find that “[h]umans with a genetic mutation do not need to have a fever to have a seizure.” *Id.* at \*\*30-32. On that basis, the Special Master implicitly rejected Petitioner’s pertussis/fever/seizure theory, because it lacked medical scientific certainty. *Id.* at \*32; *see also id.* (“[Petitioner] has been given more than one opportunity to address the experiments conducted by the Catterall group of researchers, including the studies reported by Oakley and Yu. [Petitioner] could have submitted evidence in the form of a supplemental report from Dr. Kinsbourne. Yet even after these opportunities, [Petitioner] has not presented any persuasive argument to distinguish these studies.”). In doing so, the Special Master applied the wrong standard of proof and erred as a matter of law in determining that Petitioner failed to establish a medical theory causally connecting the vaccine and the injury. *See Knudsen ex. rel Knudsen*, 35 F.3d 543, 549 (Fed. Cir. 1994) (“‘[S]cientific certainty’ is not the standard of proof[.]” (quoting *Bunting v. Sec’y of HHS*, 931 F.2d 867, 873 (Fed. Cir.1991))).

In this case, Petitioner proffered the expert medical opinion of Dr. Kinsbourne that an infant with a SCN1A mutation has a “host risk factor” to GEFS+, but an external environmental factor, such as exposure to the acellular pertussis component of the DTaP vaccine, can induce the type of febrile seizures experienced by children who later are diagnosed with GEFS+. Pet. Ex. 21 at 4-10. This theory is supported by the warning labels of the DTaP vaccine manufacturer advising that, despite detoxification, sufficient pertussis toxin may be present to trigger fever and seizures. Pet. Ex. 73 at 1 (citing Sanofi Pasteur warning labels on Daptacel® (available at <http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM103037.pdf>)). The record also establishes that after Jordan’s first febrile seizure, others followed on a regular basis. *See e.g.*, Pet. Ex. 5 (medical records from Pediatric Neurology of Hudson Valley); Pet. Ex. 19 (same); Pet. Ex. 48 (medical records from the Institute of Neurology and Neurosurgery at Saint Barnabas); Pet. Ex. 52 (same); Pet. Ex. 58 (same). The Special Master, however, found that “[t]he evidence convincingly establishes that Jordan’s first seizure did not affect his development. The primary evidence supporting this finding is [the mice experiment, reported in OAKLEY (2009) (Gov’t Ex II)].” *Harris*, 2011 WL 2446321 at \*29. Again, the Special Master misapplied the standard of proof. *See Andreu v. Sec’y of HHS*, 569 F.3d 1367, 1377 (Fed. Cir. 2009) (holding that the special master “erred in requiring . . . conclusive evidence in the medical literature linking . . . the DPT vaccine [to the petitioner’s injury],” because doing so would increase a claimant’s burden under the Vaccine Act). Instead, “[m]edical literature and epidemiological evidence must be viewed . . . not through the lens of the laboratorian, but instead from the vantage point of the Vaccine Act’s preponderant evidence standard[.]” *Id.* at 1380.

In addition, the fact that medical literature relied on by Dr. Kinsbourne regarding the necessity of a “gene-gene or environmental interaction” to induce a seizure response was contradicted by other medical literature, suggesting that mosaic parents and “spontaneous mutations in SCN1A” explain why children of asymptomatic parents nevertheless can develop



GEFS+ or another seizure disorder is not dispositive. Gov't Ex. C at 4-5. Again, only a "simple preponderance of evidence" is required, "not scientific certainty." Petitioners are not required to proffer "epidemiologic studies" or "general acceptance in the scientific or medical communities." As the United States Court of Appeals for the Federal Circuit has recognized in *Andreu*, 569 F.3d at 1378, medical literature does not attribute causation "until a level of *very near certainty*—perhaps 95% probability—is achieved." *Id.* at 1380 (internal quotation marks and citations omitted). Under the Vaccine Act, causation-in-fact is determined on a much lower standard, *i.e.*, whether causation is "*logical*" and "*legally probable*." *Id.* at 1380 (internal quotation marks and citations omitted). For these reasons, the court has determined that Petitioner has met his burden to demonstrate that it was more probable than not that the DTaP vaccine was at least a "substantial factor" in bringing about Jordan's first febrile seizure, followed by a sufficient number of other febrile seizures to be diagnosed as GEFS+. *See Althen*, 418 F.3d at 1279; *see also Shyface*, 165 F.3d at 1353 (holding that petitioner had demonstrated causation, even where the vaccine "was not the predominant cause" of petitioner's injury).

As to the logical sequence of cause and effect, Jordan's medical records show that within hours after receiving a DTaP vaccination on May 7, 2004, Jordan experienced the first of over fifty-five seizures that followed. Pet. Ex. 12 ¶¶ 5, 28.

Finally, regarding the proximate temporal relationship, the record evidences that Jordan received a DTaP vaccination on May 7, 2004 followed by "[Seizure] episode vs[.] [vaccine] reaction." Pet. Ex. 4 at 29.<sup>27</sup>

Because the Special Master acknowledged that the Petitioner's evidence on causation could be read to demonstrate causation-in-fact, Petitioner has satisfied his burden to establish, by

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<sup>27</sup> Because the court has determined that the Petitioner has established causation-in-fact, the court does not need to consider Petitioner's alternative argument that the DTaP vaccine "significantly aggravated" Jordan's preexisting condition of a SCN1A gene mutation. *See* 42 U.S.C. § 300aa-11(c)(1)(C)(ii)(I); *see also* 42 U.S.C. § 300aa-33(4) (defining "significant aggravation" as "any change for the worse in a preexisting condition which results in markedly greater disability, pain, or illness accompanied by substantial deterioration of health"). In *Whitecotton ex rel. Whitecotton v. Sec'y of HHS*, 81 F.3d 1099 (Fed Cir. 1996), the United States Court of Appeals for the Federal Circuit held that in analyzing a significant aggravation claim in the context of a Table injury, a special master must "(1) assess the person's condition prior to administration of the vaccine, (2) assess the person's current condition, and (3) determine if the person's current condition constitutes a 'significant aggravation' of the person's condition prior to vaccination within the meaning of the statute." *Id.* at 1107. The United States Court of Appeals for the Federal Circuit, however, has not yet considered a non-table case alleging "significant aggravation" causation.

This issue has been addressed, however, by the United States Court of Federal Claims in *Loving v. Sec'y of HHS*, 86 Fed. Cl. 135 (2009), wherein it was determined that the proper test was to combine the *Whitecotton* significant aggravation test with the elements identified in *Althen*. *Id.* at 144. *Loving* is on remand to the special master. Our appellate court should first have the opportunity to determine whether that analysis should be afforded precedential status.

a preponderance of the evidence, that the DTaP vaccine can be a substantial factor in causing GEFS+.

Therefore, the court's review turns to what the Special Master characterized as "the key dispute in this case" — whether the SCN1A mutation "was sufficient by itself," *i.e.*, alone, to cause Jordan's GEFS+ disorder. *Harris*, 2011 WL 2446321 at \*11.

## 2. The Special Master Erred In Finding That The Government Demonstrated Alternate Causation.

The text of the Vaccine Act presents the dispositive issue on alternative causation as whether a petitioner has established "that there is not a preponderance of the evidence that the illness, disability, injury, condition, or death described in the petition is due to factors unrelated to the administration of the vaccine described in the petition." 42 U.S.C. § 300aa-13(a)(1)(B).

There is no evidence in this record, scientific or otherwise, that establishes that a child with a SCN1A mutation, *necessarily* will develop GEFS+ or another seizure disorder. The Special Master's finding that Petitioner did not "present[] persuasive evidence" in support of his theory "that an environmental trigger is also necessary to cause symptoms" answers the wrong question. *Harris*, 2011 WL 2446321 at \*20. In the causation-in-fact analysis a petitioner need only show a connection between the vaccine and the disease in question. Having done so, the burden shifts to the Government to demonstrate alternate causation.

What the record establishes is that Jordan was born with a SCN1A gene mutation (Pet. Ex. 6 at 51), but was healthy and did not experience any seizures during the first two months of his life, until he received his first DTaP shot. Pet. Ex. 12 ¶¶ 3-5. The record also establishes that a vaccination with acellular pertussis can cause a fever. Pet. Ex. 73 at 2 (citing Sanofi Pasteur warning labels on Daptacel® (available at <http://www.fda.gov/downloads/Biologics/BloodVaccines/Vaccines/ApprovedProducts/UCM103037.pdf>)). On May 7, 2004, the day that Jordan received his first DTaP shot, he developed a febrile seizure. Pet. Ex. 12 ¶ 5. The record also evidences that GEFS+ manifests itself during the first year of life with febrile seizures. Gov't Ex. JJ at 3. The fact that Jordan's parents did not develop or display a seizure disorder strongly indicates that some other factor or factors, whether it be genetic, *i.e.*, *de novo* mutation,<sup>28</sup> or environmental, as Dr. Kinsbourne suggests, was required to induce Jordan's seizures. In addition, Dr. Raymond opined that "[w]hether a particular mutation results in disease or not is based on several lines of evidence," Gov't Ex. E at 5, and that a mutation like Jordan's has been previously reported to result in a phenotype consistent with Jordan's phenotype. TR at 450. He never, however, stated that a child with an SCN1A mutation necessarily will develop or manifest GEFS+. In fact, Dr. Raymond was "uncertain" as to why Jordan's mutation did not result in SMEI or Dravet's Syndrome in light of the factors he looks to when determining whether a mutation will be severe or not. Gov't Ex. E at 5.

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<sup>28</sup> The record shows that Jordan inherited a mutation in his SCN1A gene from his father in addition to the splice site mutation, thus creating a "state of compound heterozygosity[.]" See Pet. Ex. 9 at 35. But, Dr. Raymond noted, "the variation that Jordan and his father share is not likely a disease-causing mutation." Gov't Ex. E at 5.

In conducting the § 300aa-13(a)(1)(B) analysis, the United States Court of Appeals for the Federal Circuit has held that the Government is “required not only to prove the existence of [a preexisting condition], but *also* to prove by a preponderance of the evidence that the particular [preexisting condition] present in the child actually *caused* the . . . injury complained of.” *See Knudsen*, 35 F.3d at 549. The Government’s burden to prove alternate causation is a heavy one; once a petitioner demonstrates causation-in-fact, the Government can prevail only if it demonstrates, by a preponderance of the evidence, that a proposed alternative cause was the “*sole substantial factor in bringing about the injury.*” *De Bazan v. Sec’y of HHS*, 539 F.3d 1347, 1354 (Fed. Cir. 2008). Otherwise “a child could never recover under the Vaccine Act if the [G]overnment demonstrated that the child had a [preexisting condition] at the time of vaccination or injury.” *Knudsen*, 35 F.3d at 549-50; *see also Althen*, 418 F.3d at 1282. But, that is what happened in this case. The Special Master properly concluded that the *existence* of SCN1A mutation can be an alternative cause, but erred in finding that the SCN1A mutation “*was in fact an alternative caus[e].*” *Knudsen*, 35 F.3d. at 550.

Much of the conflict among the parties’ experts and the primary focus of the Decision Denying Entitlement, (*Harris*, 2011 WL 2446321 at \*\*16-21, 22, 25-32), concerned the interpretation and significance of 31 medical articles on a variety of relevant issues. Mutations in the SCN1A and SCN1B genes that encode the protein components of the brain sodium ion channel Na<sub>v</sub>1.1 were not discovered until 1999 and 2000. Therefore, it comes as no surprise that the influence of these gene mutations on GEFS+ and other seizure disorders continues to be debated in the academic medical community. Furthermore, it is estimated by Dr. Raymond that only 25% of children with GEFS+ have SCN1A mutations. TR at 437. Dr. Kinsbourne puts the figure even lower at only 5-10% of cases. Pet. Ex. 21 at 4. Thus the evidence is clear that the majority of GEFS+ cases are not caused by SCN1A mutations, and, moreover, it is also clear that a SCN1A mutation is not the “*sole substantial cause*” of each case of GEFS+. In other words, although there is a relationship between SCN1A gene mutations and GEFS+, a one-to-one relationship has not been established, nor has it been determined that exposing a patient with a SCN1A mutation to acellular pertussis will have no adverse consequences. *See MCINTOSH* (2010) (Gov’t Ex. VV) at 6 (“Our study design and absence of a control group of patients with [SMEI] who did not have DTP vaccinations precluded us from examining a gene-environment interaction.”). All of this academic medical debate and the Special Master’s interpretation thereof ignores a central tenant of *Althen* that “requiring medical literature . . . contravenes section 300aa-13(a)(1)’s allowance of medical opinion as proof.” *Althen*, 418 F.3d at 1280. As the United States Court of Appeals for the Federal Circuit explained in that case, requiring a medical theory to be endorsed or supported by medical literature “prevents the use of circumstantial evidence envisioned by the preponderance standard and negates the system created by Congress in which close calls regarding causation are [to be] resolved in favor of injured claimants.” *Id.* at 1280 (citing *Knudsen*, 35 F.3d at 549 (explaining “to require identification and proof of specific biological mechanisms would be inconsistent with the purpose and nature of the vaccine program”))).

The Special Master determined that Dr. Raymond’s testimony was more reliable than Dr. Kinsbourne’s, in part because Dr. Raymond was a geneticist. *See Harris*, 2011 WL 2446321 at \*\*13, 21-22. But the Special Master did not mention Dr. Kinsbourne’s explanation that, because

of his extensive training and experience as a pediatric neurologist, he, like Dr. Wiznitzer, had substantial academic and other training in gene-related disorders. Pet. Ex. 53 at 2; *see Moberly ex. rel. Moberly v. Sec’y of HHS*, 592 F.3d 1315, 1326 (2010) (“Finders of fact are entitled—indeed, expected—to make determinations as to the reliability of the evidence presented to them and, if appropriate, as to the credibility of persons presenting that evidence. *What Andreu prohibited was for the finder of fact to reject evidence based on an unduly stringent legal test while characterizing the rejection as based on the reliability of particular evidence or the credibility of a particular witness.*” (emphasis added)); *see also Porter*, 2011 WL 5840315.<sup>29</sup>

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<sup>29</sup> The court has carefully reviewed the written and oral testimony of Dr. Kinsbourne and found that his analysis and insights were helpful and instructive, as were those of the Government’s experts, Dr. Wiznitzer and Dr. Raymond. The court was impressed by the fact that all of the experts proffered by the parties had outstanding and relevant professional credentials. The Special Master, however, found that

Dr. Kinsbourne expressed opinions that are outside of his field of expertise, such as the toxoiding process. Within Dr. Kinsbourne’s *ostensible* field of expertise, pediatric neurology, he was much less knowledgeable than Dr. Wiznitzer, who continues to practice pediatric neurology.

*Harris*, 2011 WL 2446321 at \*35 (emphasis added).

Dr. Kinsbourne’s unchallenged reference to written warnings of the manufacturer of the DTaP vaccine was not an “opinion” about the “toxoiding process;” rather he simply was repeating the manufacturer’s superior knowledge about those products. In addition, and more important, the Special Master’s condescending mischaracterization of Dr. Kinsbourne’s *bona fides* is out of line. Dr. Kinsbourne is not “ostensibly” a pediatric neurologist. *See id.* at \*35. No lesser academic institutions than Oxford University, Duke University Medical Center, the University of Toronto, Harvard Medical School, Boston University, and Tufts University have recognized Dr. Kinsbourne as an expert in this field, contrary to the views of the Special Master. Pet. Ex. 22 at 1-2. The Special Master also misrepresented Dr. Kinsbourne’s current position in the New School in New York City, where he teaches neuroscience, not psychology, as the Special Master implies. *Compare id.* at 2 with *Harris*, 2011 WL 2446321 at \*4. Finally, the Special Master emphasized that Dr. Kinsbourne is “well-known” to special masters, because he testifies frequently in the Vaccine Program for petitioners. *See Harris*, 2011 WL 2446321 at \*4. Of course, the Special Master made no mention of the fact that the same is true of Dr. Wiznitzer. The Special Master’s proclivity to demean petitioners and their experts when he differs with their opinions is not required to make a credibility determination. *See e.g., Porter*, 2011 WL 5840315 at \*\*13-15 & n.4 (Fed. Cir. Nov. 22, 2011) (O’Malley, J. dissenting) (discussing this Special Master’s “remarkable” opinion for “the sheer number of references to credibility, demeanor and veracity” and character attack on an expert with whom he disagreed); *Dobrydneva v. Sec’y of HHS*, 94 Fed. Cl. 134, 147 (2010) (noting the Special Master’s “near obsession with discrediting [Petitioner’s] mother’s contemporary observations[.]”); *Campbell v. Sec’y of HHS*, 90 Fed. Cl. 369, 383-84 (2009) (the Special Masters’ misevaluation of an expert’s credibility “pervaded this analysis”). The modest hourly compensation that physicians receive for rendering a professional medical opinion, based on decades of experience, does not compensate them for *argumentum ad*

Moreover, as the United States Court of Appeals for the Federal Circuit stated in *Andreu*, the job of the fact finder is to “make[] a credibility determination . . . not to evaluate whether an expert witness’ medical theory is supported by the weight of epidemiological evidence.” 569 F.3d at 1379. Of course, that is what happened here. *See Harris*, 2011 WL 2446321 at \*\*16-23, 24-32.

Therefore, the court views the entirety of the record on alternative causation as a classic case of “conflicting” experts, a situation that the United States Court of Appeals for the Federal Circuit has stated “does not[,] in our view[,] either compel a finding of . . . alternative causation nor preclude one.” *Knudsen*, 35 F.3d at 550. When a special master is confronted with such a record, the instruction of our appellate court to the special master is clear:

If the evidence is seen in equipoise, then the government has failed in its burden of persuasion and compensation must be awarded . . . especially in view of . . . the “generosity” of the Vaccine Act.

*Id.* at 550-51.

The Special Master did not follow this directive. Accordingly, his finding that Jordan’s “epilepsy was caused by the genetic mutation” is erroneous as a matter of law, because the Government failed to meet its burden of proof to establish that the presence of a SCN1A mutation was not merely a possible alternate cause of Jordan’s first febrile seizure and GEFS+, but was, in fact, the sole cause of Jordan’s first febrile seizure and subsequent GEFS+. <sup>30</sup> Accordingly, the court finds that Jordan suffers from GEFS+ seizure disorder and that he has carried his burden to demonstrate that his condition was caused-in-fact by his DTaP vaccination. <sup>31</sup>

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*hominem* disguised as “credibility determinations.” Professional careers of physicians are built and maintained based on their reputation in the medical community and among their peers. What rational, established physician would want to risk an assault on his credentials and professional standing to render an opinion in a Vaccine Act case under these circumstances? The undersigned judge has seen other cases where knowledgeable physicians have declined to render a relevant, if not dispositive opinion, because they did not want to be subject to such “credibility determinations.” *See Record in John Doe 21 v. Sec’y of HHS*, Docket No. 02-0411V (Dr. Lydia Eviatar, M.D., Professor of Pediatric Neurology at the Long Island Campus of the Albert Einstein College of Medicine declining to testify in remand proceeding before the same special master). Allowing this unnecessary and unprofessional conduct to continue has had significant adverse consequences on the Vaccine Act Program.

<sup>30</sup> To the extent that the Special Master made a factual determination that the Government carried its heavy burden of proof, it was arbitrary and capricious, because the Special Master afforded too much weight to the Government’s evidence that GEFS+ *can*, in theory, arise absent a vaccine or a vaccine-induced fever. *See Knudsen*, 35 F.3d at 548 (“Causation in fact under the Vaccine Act is thus based on the circumstances of the particular case, having no hard and fast *per se* scientific or medical rules.”).

#### IV. CONCLUSION.

For these reasons, the court has determined that the record has established that Petitioner's Motion For Review is granted. The Special Master's Decision is reversed. This case is remanded to the Special Master for an award of compensation to the Petitioner, reasonable attorney fees, and other costs.

**IT IS SO ORDERED.**

s/ Susan G. Braden  
**SUSAN G. BRADEN**  
**Judge**

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<sup>31</sup> Jordan's "vaccine-related injury," *i.e.*, GEFS+, is the least severe of the spectrum of diseases linked to SCN1A mutation. TR at 62. A child with GEFS+ will not typically suffer developmental delay or cognitive injury. *Id.* Nonetheless, the National Vaccine Injury Compensation Act provides that a petitioner may seek to recover for a non-table "vaccine-related injury or death" so long as the patient has "suffered the residual effects or complications of such illness, disability, injury, or condition for more than 6 months after the administration of the vaccine[.]" 42 U.S.C. § 300aa-11(c)(1)(D)(i) (2006). Indeed, a prior version of § 300aa-11(c)(1)(D)(i) *did* require that the "illness, disability, injury, or condition" be severe enough such that the Petitioner "incur[] unreimbursable expenses due . . . to such illness, disability, injury, or condition in an amount greater than \$1,000." However, Congress repealed even that modest limit on monetary recovery for a vaccine-related injury over a decade ago. *See* Pub. L. No. 105-277, § 1502 (1998) (section entitled "Elimination Of Threshold Requirement Of Unreimbursable Expenses"). Accordingly, the United States Court of Federal Claims and the United States Court of Appeals for the Federal Circuit have focused not on the severity of the illness or injury, but only on whether the illness or injury is vaccine-caused and whether a petitioner has suffered for more than six months. *See, e.g., Lombardi v. Sec'y of HHS*, 656 F.3d 1343, 1354 (Fed. Cir. 2011) (holding that petitioner did not establish that she suffered from vaccine-caused Chronic Fatigue Syndrome, but never questioning that she would be entitled to compensation under the Act if causation was established); *see also Berry v. Sec'y of HHS*, No. 01-556V, 2006 WL 2848617 at \*\*15-16 (Fed. Cl. 2006) (awarding judgment to petitioner who suffered from vaccine-related chronic joint pain). Although seizures that do not lead to encephalopathy are excluded from being *table* injuries, *see* 42 C.F.R. § 100.3(b)(2)(i)(E) (listing acute encephalopathy as a table disease but noting that "[i]n the absence of other evidence . . . seizures shall not be viewed as the first symptom or manifestation of acute encephalopathy"), nothing in the text, statutory history, or case law of § 300aa-11(c)(1)(D)(i) prevents a lifelong, vaccine-caused disease or disability such as GEFS+ from being compensable. In this case, Jordan has been hospitalized on multiple occasions and will likely continue to require hospitalization and treatment for future seizures. Therefore, he is entitled to recover such medical and other expenses as are appropriate for his vaccine-caused GEFS+.